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ORIGINAL PAPER

Biological therapy in inflammatory rheumatic diseases: issues in Central and Eastern European countries

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Abstract Biological drugs revolutionized the treatment of inflammatory rheumatic diseases. Access to treatment presents substantial variability across Europe. The economic level of a particular country as well as administrative restrictions have been proved as determining factors of biological drug uptake. The objective of this paper was to provide an overview of biological treatment in six selected Central and Eastern European (CEE) countries, namely in the Bulgaria, Czech Republic, Hungary, Poland, Romania and Slovakia. The literature is summarized with regard to the epidemiology, disease burden and use of biological agents in rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis. Moreover, an estimate is provided on the prevalence and number of patients with biological treatment based on international and local sources. In view of the limited availability of information and uncertainty in data, there is an urgent need for development of systematic and comprehensive data collection in inflammatory rheumatic diseases in CEE countries.

Keywords Rheumatoid arthritis · Ankylosing spondylitis · Psoriatic arthritis · Biological therapy · Health services accessibility · Central and Eastern Europe

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Background

This Supplement of The European Journal of Health Economics deals with issues around biological and biosimilar drug treatment of chronic inflammatory diseases in the field of rheumatology, gastroenterology and dermatology in the Central and Eastern Europe (CEE) region. In this paper we present briefly the three inflammatory rheumatic conditions (rheumatoid arhritis, RA; ankylosing spondylitis, AS; psoriatic arthritis, PsA) the Supplement is focusing on. We also provide a review on the epidemiology, disease burden and access to biological drug treatment in these three rheumatic disorders based on literature data, with special

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focus on Bulgaria, Czech Republic, Hungary, Poland, Romania and Slovakia.

Introduction to inflammatory rheumatic diseases

RA is a chronic inflammatory disease characterized by swelling, tenderness and destruction of joints, leading to severe functional disability, lowered quality of life and premature mortality [1]. Besides pain, stiffness, limited motion and function of many joints, RA is frequently accompanied by a variety of extra-articular manifestations (e.g. rheumatoid nodules, lung involvement and vasculitis) due to its systemic character. Moreover, patients often experience fatigue, and depression is also highly prevalent [2, 3]. RA is often associated with severe co-morbidities such as osteoporosis, infections and furthermore, accelerated atherosclerosis and cardiovascular diseases are leading causes of increased mortality in RA [4]. RA is known to reduce the lifespan of patients by about 10 years and according to data from RA registries, the mortality of the disease has not changed over the past 20 years despite the advances in RA therapy [5]. Overall, RA represents a significant clinical and economic burden for patients, health care systems and societies.

AS is the major subtype and a main outcome of an interrelated group of rheumatic diseases named spondyloarthritis (SpA) [6]. Back pain is the leading clinical symptom in AS, especially in the predominantly axial subgroup (named axial SpA including AS and non-radiographic axial SpA), as the disease is characterized by spinal stiffness and loss of spinal mobility, which are explained by spinal inflammation, structural damage, or both. In the peripheral form, arthritis affects usually one or a few joints and appears mainly but not exclusively in the lower limbs. The disease may involve eye, gut and aorta. The most common extra-articular manifestations in AS are represented by uveitis (inflammation of the pigmented vascular part of the eye), inflammatory bowel disease, heart, lung, skin, bone and kidney involvement [7]. Patients with symptomatic AS lose productivity, triggering work disability and unemployment, have a substantial use of health care resources, and reduced quality of life [8].

PsA is one of the subsets of SpA [9]. PsA is characterized by heterogeneous clinical domains, arthritis, inflammation of insertions of tendons, ligaments and joint capsule fibers to bone (enthesitis), swelling of a whole digit (dactylitis), inflammation of the spine, psoriasis and nail disease. Persistent inflammation from PsA can lead to joint damage and functional disability in patients with PsA and may result in significant impairment of quality of life, psychosocial disability and productivity loss [10]. There appears to be a greater incidence of cardiovascular death in psoriatic disease, especially in more severe cases [11].

Although juvenile idiopathic arthritis (JIA) is out of the main scope of this review, it is critical to mention this rheumatic condition as well. JIA occurs in patients aged <16 years and includes several types of arthritis [12]. Some of the biological agents have been registered for the treatment of JIA and the transfer of patients from pediatric to adult care is a point to consider in rheumatology.

Epidemiology

The challenges of descriptive epidemiology of inflammatory rheumatic diseases are common to chronic and complex diseases [13]. One major challenge is to identify when the inflammatory rheumatic disease actually starts. Some patients might be in remission at the time of the prevalence survey or, on the contrary, not diagnosed. Furthermore, classification criteria have changed in the past decade with the better understanding of disease pathogenesis, development of more sensitive laboratory markers, new imaging techniques and effective targeted treatments. In RA, for instance, aggressive therapy with disease-modifying antirheumatic drugs (DMARD) in the early stage of the disease has proven to be a successful strategy for preventing joint damage and achieving optimal clinical outcomes. However, the American College of Rheumatology (ACR) 1987 criteria which had been used for decades to classify the disease, failed to identify individuals with very early arthritis who subsequently develop RA. Thus, the new 2010 ACR/EULAR classification criteria for RA were developed using initiation of methotrexate (a conventional synthetic DMARD, csDMARD) as anchor in a population with undifferentiated arthritis [1]. A similar shift has occurred in the classification of SpA [14]. These advances, however, make epidemiological counts difficult and lack of use of uniform recruitment criteria across studies hampers the comparability of results from the past decades.

Rheumatoid arthritis

Although RA may be present at any age among adults, patients most commonly are first affected in the third–sixth decades. Prevalence rises with age and is highest in women over 65 years. The median annual incidence of RA in the south European countries is 16.5 (range 9–24) cases per 100,000 and in the north European countries 29 (range 24–36) per 100,000 [15]. The median prevalence estimate for the total population in south European countries is 3.3 (3.1–5.0) and for north European countries is 5.0 (4.4–8.0) cases per 1,000 people.

The prevalence of RA among individuals aged 14–65 years was 0.37 % according to a population-based survey in Hungary [16]. In the Czech Republic (2002–2003) the prevalence of RA was 610 (95 % CI 561–658) per 100,000 and the annual incidence of RA was 31 (95 % CI 20–42) per 100,000 in the adult population aged ≥16 years [17].

In Hungary, the National Health Insurance Fund Administration (NHIFA) covers the whole population, thus its database can be used as an excellent source for specific epidemiological studies [18, 19]. Analysis of the NHIFA data confirmed a prevalence of 0.5 % (year 2002); however, the number of RA patients who have had at least one outpatient rheumatology visit per calendar year was 30,996 in 1999 and 30,841 in 2000, and the total for the 2-year period was 48,614 RA patients [20]. The number of RA patients who had more than one outpatient rheumatology visit per calendar year was 12,819 in 1999 and 13,115 in 2000. Héjj found similar rates in 2004 and 2005 [21]. Considering that DMARD prescription requires regular visits to rheumatologists we might assume that either the number of untreated patients is high or the 0.5 % prevalence is an overestimation—or probably a combination of both. The analysis of drug sales data appears to support these assumptions as csDMARD consumption covered only approximately 10,000–15,000 patient-years. Probably there are several reasons for the low attendance to specialized care. It is worthy of note that the phenomenon of non-participation is present in other health care areas as well in Hungary [22, 23].

Ankylosing spondylitis

The estimated prevalence of AS is 23.8 per 10,000 in Europe and the estimated number of cases is 1.3–1.5 million according to a recent literature review [24]. In the Czech Republic a population-based study showed that the annual incidence of AS in adults was 6.4/100,000 (95 % CI 3.3–11.3) and the prevalence was 94.2/100,000 (95 % CI 80.8–109.2) [25]. In Romania, some epidemiological analyses are available from Iasy County and an increasing prevalence of AS was observed between 1990 and 2006 [26, 27].

Psoriatic arthritis

The prevalence of PsA shows variations among countries and regions. Substantial disparities can be observed in the estimates of incidence (from 3.02 to 23.1 cases per 100,000 people) and prevalence (from 49.1 to 420 cases per 100,000 people) of PsA around the globe. It seems that the prevalence of psoriasis in the general population is approximately 2–3 %, with about a third of patients with psoriasis having arthritis, thus PsA may affect about 0.3–1.0 % of the population [28]. Population survey data from the Czech Republic shows that the annual incidence of PsA in adults aged ≥16 years was 3.6/100,000 (95 % CI 1.4–7.6) and the prevalence was 49.1/100,000 (95 % CI 39.5–60.4) [25].

Table 1 Estimated number of patients with RA, AS and PsA in the population with age ≥16 years in 6 CEE countries, 2013

Countries	Rheumatoid arthritis (RA)	Ankylosing spondylitis (AS)	Psoriatic arthritis (PsA)	Total
Bulgaria	38,000	5,900	3,100	47,000
Czech Republic	54,100	8,400	4,300	66,800
Hungary	50,800	7,800	4,100	62,700
Poland	197,200	30,500	15,800	243,500
Romania	101,600	15,700	8,200	125,500
Slovakia	27,600	4,300	2,200	34,100
Total	469,300	72,600	37,700	579,600

Data sources: Size of the population aged ≥16 years: Eurostat Statistics Database, 2013 [66]; prevalence rates, ≥16 years: RA 610/100,000 [17]; AS 94.2/100,000 [25]; PsA 49.1/100,000 [25]. Results were rounded to 100

On the one hand, these literature data highlight a great variance in both incidence and prevalence across the studies in all three inflammatory rheumatic diseases. On the other hand, there is a lack of epidemiological studies focusing specifically on CEE countries [15, 29]. We found no epidemiology data on RA, AS or PsA from Bulgaria, Poland or Slovakia on PubMed. In Table 1, we provide an estimate on the number of patients in the six CEE countries by extrapolation of literature data.

It is important to point out the uncertainty in our estimates. For instance, if we calculate with the prevalence rate of 0.5 % in RA for the total population [20] the patient number will be 458,400 in the six CEE countries. The estimated prevalence published by Lundkvist et al. [30] (2006) was higher, as they counted a total of 617,000 RA patients (Bulgaria: 51,000, Czech Republic 68,000; Hungary: 67,000; Poland 252,000; Romania 143,000; Slovakia: 36,000). Considering the substantial costs of the disease, even small inaccuracies in epidemiologic data will lead to robust bias in the estimation of disease related expenditures both at the national and regional (CEE) levels. Therefore, there is a need to perform more epidemiologic research in the CEE region to provide comparable and more detailed data for health care planning. At the same time, we might assume that overall there are about half a million patients with RA, AS or PsA in the six CEE countries.

Disease burden

Rheumatoid arthritis (RA)

The burden of RA appears to correlate substantially with socioeconomic and health care system related factors, i.e. GDP and access to treatment in a specific country [30, 31]. Productivity loss and work disability is a major problem in RA even today [32].

In Western European countries health care bears an annual cost of over €4,000 per patient: the cost to patients and families is more than €2,000 yearly [33]. In studies of biological therapies (namely anti-tumour necrosis factor-alpha, anti-TNF agents), the drug costs were higher but the overall costs were lower with these agents. Costs related to lost productivity are highly dependent on the methodological approach; however, this can be 50 % higher than direct medical costs among patients without biological therapy [34].

Cost-of-illness data are scarce in the CEE region. The estimated average yearly cost per patient in a paper by Lundkvist et al. [30] (2006) were as follows: Bulgaria €2,825, Czech Republic €5,924, Hungary €5,703, Poland €5,633, Romania €4,333, Slovakia €5,022. In Hungary, a cross-sectional survey of 255 RA patients without biological treatment (in 2004) revealed an average yearly cost of €4,173 (SD 3,379) per patient, which was nearly equivalent to the direct costs of RA in Western European countries [34]. Similar health care utilisation rates were found in a subsequent study in Hungary, in 2009, among biological treatment-naïve RA patients at the time of initiation of first biological treatment (2004 vs 2009, GP visits: 79 vs 77 %; hospitalisation: 63 vs 50 %; informal care: 50 vs 66 %, disability pensioner: 50 vs 47 %) [35].

Ankylosing spondylitis (AS)

AS can have important socioeconomic consequences for both individual patients and society. AS-related sick leave in patients at work varies between 6.5 and 18 days per patient per year and between 15 and 20 % of AS patients require help from relatives or other people [36]. Cost-of-illness studies are available from a number of countries, including the Czech Republic in the CEE region. Studies on direct and indirect costs report highly diverse cost values but each agree that the societal impact of AS is mainly related to loss of productivity. The most important predictor for high costs both in the 1st and in the 5th year of the disease is functional disability [37]. In the Czech Republic, data from two cross-sectional studies (called Beda I, 2005, $N = 1{,}008$; and Beda II, 2008, $N = 509$) were analyzed. The mean total annual costs per patient in the sample were €4,782 in Beda I and €5,806 in Beda II; the average direct costs per patient per year are estimated at €1,812 (Beda I) and €2,588 (Beda II). The largest direct cost burdens were spa procedures (45.3 %, Beda I) and biological drugs (52.8 %, Beda II) [38]. In Hungary, physiotherapy is recommended in AS; however, little is known about its share of the NHIFA supported spa and outpatient physiotherapy treatments. In 2011, the NHIFA spent €17.9 million on these two types of care in all diagnoses (€1 = 279 HUF) [39]. For comparison, NHIFA expenditure on biological drugs for the treatment of AS and PsA patients was €15.5 million in 2010 (AS: €11.087 million; PsA: €4.457 million; €1 = 300 HUF) in Hungary [40].

Psoriatic arthritis (PsA)

Very few large-scale, prospective, observational studies have been conducted in PsA and only a few collected data on economic outcomes or patients' preference based quality of life scores (utilities) [41]. In Germany, mean annual per patient direct cost in PsA was €3,156 and the indirect cost varied from €2,414 to €7,919, depending on the costing method used. Disease activity and impairment of physical functions were found to be the main cost drivers [42]. According to Brodszky and colleagues, direct medical, direct non-medical, indirect and total costs in PsA (year 2008) in Hungary were (mean) €1,876, €794, €2,904 and €5,574 per patient per year, respectively. Total costs were in significant linear relationship with functional deterioration and skin severity [43].

Access to biological therapy

Currently, the following biological drugs have registration by the European Medicines Agency (EMA) for the treatment of the three inflammatory rheumatic diseases in focus: (a) eight biological agents for the treatment of RA (abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, rituximab and tocilizumab); (b) five for the treatment of AS (adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab) and six for PsA (same as in AS and in addition ustekinumab). Anakinra also has EMA registration for the treatment of RA but practically this drug is not used in the CEE region. Biosimilar infliximab has recently been registered for the treatment of the same disorders as the originator infliximab.

To give an insight into financing, findings on reimbursement and challenges of health technology assessment in CEE countries have been provided elsewhere [44, 45]. Biological treatment is reimbursed by health insurance in CEE countries and the therapy is available for patients under 100 % coverage in CEE countries (share of coverage

between the company and insurance fund occurs in several countries). Nevertheless, not all biological drugs are financed in all diagnoses. For instance, in Romania only four biological agents (infliximab, adalimumab, etanercept and rituximab) were 100 % reimbursed by the end of 2013. Geographical accessibility to specialized centers entitled to administer biological treatment appears fair enough as treatment is provided in 6 centers in Bulgaria, 28 centers in the Czech Republic,[1] 21 centers in Hungary, about 100 centers in Poland, more than 50 centers in Romania and about 6 centers in Slovakia. Nevertheless, access to treatment may vary within a country as well. For instance, the amount of funds allocated for biological therapy contracts differ in various parts of Poland, and these differences cannot be accounted for either by the population or epidemiological data in a given region [46]. Overall, due to various reasons, there are substantial differences in the access to biological treatment across the six CEE countries.

A study by Jönsson et al. [47] was among the firsts to analyze the uptake of new biological agents in RA covering the period between 2000 and 2006. They found considerable differences within Europe, and CEE countries had very limited uptake at the time of the assessment. Health care expenditure per capita was considered a major factor for determining the use in low- and middle-income countries. However, there were also significant variations between countries with similar economic conditions. Authors highlighted that determinants of access to treatments in RA include various other factors such as approval, pricing, funding, market access, as well as access to rheumatologists, recommendations, national preferences and priorities for certain drugs [48].

In 2009, analysis of biological treatment use in RA by Orlewska and colleagues considered the number of RA patients receiving biological therapy as well as the proportion of RA patients they represent, plus sales data in 11 selected CEE countries [31]. According to their results, the rate of patients on biological treatment in 2009 was the highest in Hungary (5 %), lower percentages were found in Slovakia (3.5 %), Czech Republic (2.9 %), Romania (2.2 %), and Poland (<1.5 %). In general, national guidelines defined the eligibility criteria for biological treatment.

Putrik et al. [49] performed an analysis regarding access to treatment in RA across the 46 countries of geographical Europe. They found some variations in the eligibility criteria for biological treatment between the six CEE countries. For instance, in the Czech Republic and Slovakia moderate disease activity was required for the initiation of biological treatment whilst in Bulgaria, Hungary, Poland and Romania high disease activity was set up as a rule. In certain countries, some further specific exceptions were introduced, e.g. in Poland moderate disease activity (DAS28: 3.7) was sufficient if the joints of the lower limbs were involved. The six countries also differed in terms of the required number of csDMARDs (including methotrexate) that failed before the initiation of biological treatment (Romania: two csDMARDs [50, 51]; Hungary, financial guideline: combination of two csDMARDs, clinical guideline: one csDMARD). Despite these smaller differences within the six countries, the CEE region ranked in the middle compared to the whole geographical Europe based on a composite score for restrictiveness of clinical criteria for initiation of a first reimbursed biological agent. Criteria for initiation of a biological drug were negatively associated with the countries' socioeconomic welfare [52].

The QUEST-RA study involving RA cohorts from 25 European countries also highlighted the disparities between the health status of RA patients and GDP [53]. The use of biological drugs was significantly higher in high income countries compared to low income countries. Nevertheless, the difference in GDP accounts for disease activity levels to a higher extent than currently taking or not taking csDMARDs, corticosteroid drugs and/or biological agents. Accordingly, life-expectancy and health status of the general population is better in economically more developed countries, and this gap between Western Europe and CEE countries was observed in other chronic illnesses as well [54].

Scarcity of data from patient registries in CEE countries is one of the major obstacles to the estimation of the number of treated patients and, more importantly, to the assessment of treatment patterns and patient characteristics, including relevant markers for personalized treatment [55]. Analysis of registry data have been published in the Czech Republic [56–58] and multicenter studies provide insight into selected patient cohorts [59]. A national registry of RA patients in Romania was initiated in 2013 to collect real-life data on the long-term safety of biological therapies and their impact on disease progression. By the end of 2013, data for 4,153 patients with RA treated with biological agents were available in the registry. Important analyses appeared from single center studies [60–65]; however, their value lags far behind well designed, systematically collected clinical registries. An analysis of the first 5 years (2006–2010) of reimbursed biological treatment in Hungary based on the health insurance (NHIFA) database revealed important economic aspects (patient numbers, costs, market share, first choice treatment) of biological uptake in the country [40]. However, a compulsory systematic data collection (electronic patient registry on a national level) monitoring clinical aspects and employment status of patients with biological treatment was introduced only in 2012 and results have not been published so far. The number of patients treated with biological drugs,

[1] Source: ATTRA registry, available at www.attra.registry.cz.

Table 2 Estimated numbers of patients with RA, AS or PsA treated with biological drugs in six CEE countries, 2013

Disease/country	Abatacept	Adalimumab	Certolizumab pegol	Etanercept	Golimumab	Infliximab	Rituximab	Tocilizumab	Total
Rheumatoid arthritis									
Bulgaria[a]	0	256	112	226	61	0	22	302	979
Czech Republic[b]	131	630	182	518	197	206	256	175	2,295
Hungary[c]	2	905	720	933	452	318	419	816	4,565
Poland[d]	0	494	212	855	0	123	584	301	2569
Romania[e]	0	850	0	1,210	0	426	1,667	0	4,153
Slovakia[f]	20	920	150	455	150	570	150	350	2,765
Total	153	4,055	1,376	4,197	860	1,643	3,098	1,944	17,326
Ankylosing spondylitis									
Bulgaria[a]	–	313	0	318	135	0	–	–	766
Czech Republic[f]	–	80	0	70	20	90	–	–	260
Hungary[c]	–	686	0	483	392	394	–	–	1,955
Poland[d]	–	452	0	729	0	80	–	–	1,261
Romania[e]	–	1,005	0	934	0	641	–	–	2,580
Slovakia[f]	–	95	0	55	60	55	–	–	265
Total	–	2,631	0	2,589	607	1,260	–	–	7,087
Psoriatic arthritis									
Bulgaria[a]	–	119	0	122	35	0	–	–	276
Czech Republic[f]	–	45	0	30	15	60	–	–	150
Hungary[c]	–	318	0	213	195	168	–	–	894
Poland[d]	–	410	0	143	28	0	–	–	581
Romania[e]	–	368	0	344	0	257	–	–	969
Slovakia[f]	–	90	0	85	60	90	–	–	325
Total	–	1,350	0	937	305	603	–	–	3,195

Biosimilar infliximab was registered for the treatment of RA, AS and PsA and ustekinumab for PsA in September 2013, therefore, these drugs were not included in this Table

– Not available

[a] National Health Insurance Fund data, accessed in December, 2013

[b] Czech ATTRA registry for RA, accessed in May, 2013

[c] National Health Insurance Fund Administration (NHIFA) database, accessed November, 2013. The number of JIA patients treated with biological drugs was 317 patients

[d] Accessed in November 2013. The number of JIA patients treated with biological drugs was 516 patients [67]

[e] National Registry, accessed at the end of 2013

[f] Estimation based on various sources

therefore, can only be estimated for the six CEE countries. We used multiple sources such as IMS sales statistics,[2] Ministry of Health, NHIFA, national professional societies, registries and personal communication for the estimation. The estimated numbers of patients treated with biological therapy are presented in Table 2.

The proportion of patients treated with biological agents varies significantly between CEE countries. The rate of RA patients with biological treatment based on data from Tables 1 and 2 is as follows: Bulgaria 2.6 %, Czech Republic 4.2 %, Hungary 8.4 %, Poland 1.3 %, Romania 4.1 % and Slovakia 10.0 %. Nonetheless, it is important to highlight two points. First, we had to rely on estimates in the case of Slovakia with regard to the number of RA patients treated with biological drugs. Second, prevalence data from the Czech Republic (2002–2003) were applied for the calculation in all six countries. If we consider an RA prevalence of 0.5 % (40,500 RA patients) among adults aged ≥18 years in Hungary according to local NHIFA data [20] the treatment rate increases to 11 %. Moreover, the number of RA patients attending regular rheumatology care is only about half of the RA prevalence in Hungary.

[2] The validity of IMS data are not known due to the fact that IMS data covers the retail channel only, a number of companies deliver products directly to hospitals without other distribution channels, and secondly a significant proportion of biologicals are re-exported (parallel export).

Consequently, considering only this subsample of RA patients who follow the clinical guidelines would result in a 2 times higher biological treatment rate. Presumably a similar gap exists between prevalence and regular care rates in the other five CEE countries as well. Therefore, the question arises as to whether estimates on the potential number of new patients for biological treatment should rely on prevalence data (increasing the recruitment of untreated patients) or rather on incidence data (involving newly diagnosed patients who did not respond to csDMARDs) if the regulations remain unchanged. Assessing the biological treatment rate for AS and PsA would be even more difficult due to uncertainties in input data.

Conclusions

Literature data suggest that RA patients, in general, are in a poorer state of health in CEE countries than in Western European countries, and one potential explanatory factor is the slower and more limited uptake of biological treatments. Despite the centralized drug registration and clinical guidelines at a European level, there is a significant variation in financing practices across Europe. Not even CEE countries can be considered as a homogeneous group, as there are substantial differences in the eligibility criteria for reimbursed biological treatment and in the number of available reimbursed biological drugs.

In certain CEE countries some progress has been made in developing systematic data collection. Nevertheless, the shortage of published data both in terms of epidemiology, disease burden and treatment patterns in CEE countries is still a major conclusion of our review. The scarcity of valid basic input data for clinical analyses and health economic evaluations is especially true for PsA and AS.

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